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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,611	03/22/2004	Mary Collins	01997.043200	2470

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,611	COLLINS ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 29-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 29-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/22/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/24/04, 5/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application Election/Restrictions

Applicant's election without traverse of Group I and antibody and IFN-1α/β in the reply filed on August 23, 2006 is acknowledged.

Claims 1-49 are pending. Claims 20-28 and 41-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 23, 2006. Upon reconsideration, the requirement of species election on IL-21/IL-21R agonist is withdrawn. The subject matter to the extent of IL-21 polypeptide will be included in this examination. Claims 1-19 and 29-40 are under examination in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 29-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing production of IL-10 and decreasing INF-γ and other cytokines as listed in table 3 and increasing T cell proliferation in an EAE animal model by administering to cells or animals with the IL-21 polypeptide of SEQ ID NO:2 to decrease the severity of symptoms that are regulated by inappropriate

cytokine production, does not reasonably provide enablement for ameliorating all symptoms of multiple sclerosis or modulating other disorders associated with an IL-10 deficiency or for preventing any immunological disorder by administering to a subject with an agonist of IL-21/IL-21R as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1-15 and 29-33 are drawn to a method of ameliorating a symptom of multiple sclerosis in a subject comprising administering to the subject an agonist of IL-21/IL-21R wherein the agonist is IL-21 or an agonistic IL-21R antibody/antigen-binding fragment thereof. Claims 16-19 are directed to a method of ameliorating a symptom of multiple sclerosis in a subject and further comprising evaluating a subject for risk of multiple sclerosis by evaluating the level of IL-10 prior to the administration of the agonist. Claim 34 is directed to a method of modulating an IL-10 deficiency or a disorder associated with an IL-10 deficiency by administering to a subject with an IL-21 polypeptide to increase the expression or activity of IL-10 in the subject. Claims 35-40 are directed to a method of treating or preventing an immunological disorder in a mammal subject by evaluating an IL-10 parameter and administration of an IL-21 polypeptide to the subject.

Applicant describes that IL-21 can induce T cell proliferation and increase IL-10 production and decrease IFN-γ in cells derived from lymph nodes and treated with MOG 35-55 in vitro. Applicant also describes that administration of an IL-21 polypeptide of SEQ ID NO:2 can reduce the severity of an EAE animal model induced by PLP139-151 plus petussis toxin (one of animal models for multiple sclerosis). Applicant further describes that IL-10 is upregulated and IFN-γ and other cytokines as listed in table 3 are downregulated in the EAE animal model.

Based on the specification and the prior art, Applicant is enabled for increasing the level of IL-10 expression and decreasing the secretion of IFN-γ and other cytokines as in table 3 in vitro and in vivo by administration of the IL-21 polypeptide of SEQ ID

NO:2 to a subject. Thus, it is predictable that Applicant is enabled to reduce the symptom that is regulated by IL-10 and IFN-γ and other cytokines listed in table 3 by administration of IL-21 to the patients. However, Applicant fails to provide sufficient guidance as to whether administration of any agonist IL21R antibody could achieve the same results as SEQ ID NO:2 in increasing IL-10 and decreasing IFN-γ since the mechanisms of the activation of a receptor (IL21R) by an agonist antibody (anti-ILR antibody) are different from regular antibodies (antagonistic or neutralizing antibodies) and is also based on the binding activity of the antibody to the receptor and also to the specific site of the receptor; for example, the binding affinity of anti-IL21R antibody to IL21R (Ledbetter et al. Circ. Shock. 1994. 44: 67-72). Thus, it is unpredictable whether any agonist anti-IL21R antibody would function the same as IL-21 with the amino acid sequence of SEQ ID NO:2 (the ligand of IL-21R). In addition, Applicant defines an IL-21 polypeptide as including fragments of IL-21 and homologues with 30-95% identity to SEQ ID NO:2 on p. 18-20. However, Applicant fails to teach whether any fragment would have the same effect as the full length of SEQ ID NO:2. Applicant fails to teach what specific regions of SEQ ID NO:2 would be required to maintain the activity of IL-21 in ameliorating MS. Thus, it is unpredictable whether any IL-21 polypeptide or agonist with at least 90-95% identity to SEQ ID NO:2 as in claims 1-4 would function as SEQ ID NO:2 in increasing IL-10 and decreasing IFN-γ or inducing T cell proliferation.

Based on the specification and the prior art, Applicant is predictably enabled to reduce the symptom that is regulated by IL-10 and IFN-γ and other cytokines listed in table 3 by administration of IL-21 to the patients. However, Applicant fails to provide

sufficient guidance or working examples as to how to apply the findings derived from the EAE mouse model and in vitro to ameliorating all symptoms in multiple sclerosis as recited in claim 1, all disorders associated with an IL-10 deficiency as recited in claim 34 or treating/preventing all immunological disorder as recited in claims 35, 38 and 40 since the cause of multiple sclerosis is complex and the cause of all disorders associated with an deficiency of IL-10 and all immunological disorders are unknown. MS is characterized as an autoimmune disorder mainly affecting young adults and characterized by destruction of myelin in the central nervous system and its pathologic findings include demyelination throughout the white matter of the central nervous system. One of potential mechanisms for MS has been proposed as that it is an autoimmune disease of TH-1 type cell mediated immune response against myelin sheath, which subsequently results in inflammation and degeneration in the nervous system. In addition, the pathology of MS is very heterogeneous. It has been shown that at least four different patterns of pathology in MS. Patterns I and II can be shown close similarity in the animal model of experimental autoimmune encephalomyelitis (EAE), where the lesions are induced by autoreactive T cells and autoantibodies (see p. 375, first paragraph, 't Hart et al. Curr. Opin. Neurol. 2003. 16: 375-383). 't Hart et al. also showed that the animal models for MS can not truly reflect the pathogenic mechanisms of MS. Each animal model only has partial clinical aspects and histopathology of MS, indicating that the effects shown in one MS mouse model does not truly reflect the end results in patients with different forms of MS. Although it has been shown that injection of MBP into mice can induce experimental allergic encephalomyelitis (EAE), which

subsequently initiates a cascade of immune-mediate damages, the cause of MS is still not established. Since Applicant has provided no guidance on applying the findings of the EAE mouse mode and the findings of in vitro to how to use a method of ameliorating all forms of multiple sclerosis or all immunological disorders, it is unpredictable whether administering any IL-21 polypeptide of SEQ ID NO:2 or an agonistic IL-21R antibody could ameliorating/treating/preventing any diseases as mentioned above, indicating that undue experimentation is required.

Since neither the specification nor the prior art has taught the cause of all forms of MS, it is unpredictable whether administration of IL-21 polypeptide could achieve the goal of ameliorating all symptoms of multiple sclerosis. In addition, since the cause of all disorders associated with an IL-10 deficiency or all immunological disorders as recited in claims 35, 38 and 40 is unknown, it is also unpredictable whether administration of all IL-21 polypeptides or all agonistic anti-IL21R antibodies would be able to modulate all disorders associated with an IL-10 deficiency or treat/prevent all immunological disorders. Applicant has not provided sufficient guidance as to enable one of ordinary skill in the art as to how to use the claimed invention since the outcome of using these agonists of IL-21/IL-21R as recited in the claims are unpredictable. Without knowing the full scope of etiology and molecular mechanisms underlying MS or all disorders associated with an IL-10 deficiency or all immunological disorders, it is unpredictable whether the administration of an IL-21 polypeptide or agonist anti-IL21R antibody could ameliorating all symptoms of MS or treating/preventing all immunological disorders,

indicating that undue experimentation is required for one of ordinary skill in the art to practice the claimed invention.

In addition, claims 16- 19 recite evaluating an IL-10 parameter to evaluate whether a subject is at risk of MS. Claims 35-40 are directed to a method of treating or preventing an immunological disorder in a mammal subject by evaluating an IL-10 parameter and administration of IL-21 polypeptide to the subject. Applicant fails to provide sufficient guidance as to how to identify whether a subject is at risk of MS by evaluating IL-10. Although IL-10 has been shown to have an anti-inflammatory and immunosuppressive effect on pro-inflammatory function of T helper cells and natural killer cells and low production of IL-10 has been found in chronic EAE and MS, overproduction or inappropriate production of IL-10 also play a role in other autoimmune diseases such as systemic lupus erythematosus (SLE) and myasthenia gravis (see p. 408, 1st col. 2nd-3rd paragraphs, Beebe et al. Cytokine and Growth Factor Rev. 2002. 13: 403-412 as in IDS). The production of IL-10 is higher in patients with SLE (see p. 405, 2nd col. 1st paragraph to 2nd paragraph). Applicant fails to provide sufficient guidance as to how to evaluate whether a subject is at risk of MS by evaluating any IL-10 parameter. Although Applicant describes several assays to evaluate the IL-10 activity on cellular function of T/B lymphocytes, Applicant fails to teach how to determine what parameter could be used to determined as an IL-10 parameter and decide if a subject is at risk. Furthermore, Claims 35-40 recite a method of preventing an immunological disorder. Claim 38 recites that the immunological disorder is a neurological disorder. However, Applicant fails to provide sufficient guidance as to what specific immunological disorders

or neurological disorders are and would be effectively treated by all IL-21 polypeptides since an immunological disorder that is also a neurological disorder could be any autoimmune disorder against neurons such as Alzheimer's disease because patients with Alzheimer's disease develop auto-antibodies against Aβ (anti-Aβ antibodies). In addition, Applicant fails to provide sufficient guidance as to how to prevent a person from any immunological disorder by evaluating IL-10 and administering IL-21 since each one of us are susceptible to any immunological disorder. Since Applicant fails to limit the immunological disorder in claims 35, 38 and 40, it is also unpredictable whether administration of IL-21 could treat or prevent the disease.

Moreover, Applicant has not provided guidance as to how to use nonhuman antibodies as recited in the claims to treat/prevent the disease. It is known in the art that a human develops anti-mouse antibodies while using immunotherapeutic approaches, which subsequently results in adverse effects, such as inflammation caused by the immune response against non-human antibodies. Applicant has not taught how to use nonhuman antibodies in ameliorating all symptoms of MS or treat/prevent all immunological disorders, indicating that undue experimentation is required for a skilled artisan to practice the claimed invention.

The instant specification has not enabled one of skill in the art to use all agonists of IL-21/IL-21R including all IL-21 polypeptides with limited homology and all agonistic anti-IL21R antibodies to treat all forms of MS and all immunological disorders, which the causes of diseases are very heterogeneous. Therefore, it would require more research and undue experimentation to understand the cause of all immunological disorders as

recited in claims 35, 38, 40 and the cause of all forms of MS first and further provide guidance as to enable one of ordinary skill in the art to practice the claimed method to potentially treat the diseases. Since the cause of the disease is still unknown and the outcomes of using the claimed method are unpredictable, the artisan would require further guidance to use the claimed method to ameliorate all symptoms of MS or immunological diseases with an expectation of success. Therefore, in view of the breath of claims, the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of ameliorating all symptoms of MS by administration of an agonist of IL21/IL21R including an IL-21 polypeptide and an agonistic IL21R antibody or IL-21 polypeptide and evaluating the risk of MS by evaluating the level of IL-10. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claims 1-3, 29-30, 34-40 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 1-3, 29-30, 34-30 recite a IL-21 polypeptide and a sequence at least 90% or 95% identical to SEQ ID NO:2 that is able to bind to an IL21R to be used in the claimed method in the claims. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is in possession of and what Applicant is claiming. From the specification, it is clear that Applicant is in possession of SEQ ID NO:2/4. However, the claims are drawn not only to the full length polypeptide but also to sequences with at least 90% or 95% identical to SEQ ID NO:2. In addition, Applicant describes that an IL-21 polypeptide on p18-20, [0048] of the specification includes SEQ ID NO:2/4 and fragments as well as proteins and fragments with at least 85% homologous to SEQ ID NO:2/4. The specification only describes SEQ ID NOs:2/4 and fails to teach or describe any other related proteins with limited homology that could be used in the claimed method. In this case, the only factor present in the claim is any IL-21 polypeptide and a partial structure in the form of a recitation of sequence similarity or percent identity. There is not even identification of any particular portion of the structure that must be conserved. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. While a generic sequence is provided, there is merely a set of common

properties: there is no description of the conserved regions which are critical to the function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function; i.e. there is no guidance of structural features that could distinguish the polypeptides in the genus from other polypeptides that are missing from the disclosure. Since the common characteristics/features of an IL-21 polypeptide are unknown, a skilled artisan can not contemplate the functional correlations of the genus with the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a method of ameliorating a symptom of multiple sclerosis in a subject comprising administering to the subject an agonist of IL-21/IL-21R, a method of ameliorating a symptom of multiple sclerosis in a subject and further evaluating a subject for risk of multiple sclerosis, a method of modulating an IL-10 deficiency or a disorder associated with an IL-10 deficiency and a method of treating or preventing an immunological disorder in a mammal subject by evaluating an IL-10 parameter and administration of an IL-21 polypeptide to the subject have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 16-19 and 34-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-19, 35 are indefinite because Applicant recites an IL-10 parameter in the claims. Although Applicant describes several assays to evaluate IL-10 activity, Applicant fails to limit what specific parameter and activity of IL-10 are and thus would be included in the limitation of the claims. The disclosure also fails to set for the metes and bounds of what is encompassed within the definition of "an IL-10 parameter". Thus the artisan would not know what responses Applicant intended to measure.

Claims 34, 37 are indefinite because Applicant recites "activity" in claims 34 and 37, and a disorder associated with an IL-10 deficiency in claim 34. Although Applicant describes several assays to measure IL-10 activity on p. 46 and few examples of a disorder associated with an IL-10 deficiency on p. 8 of the specification, these descriptions are not definite: there is no limitation on what would or would not be considered as an "activity" or "a disorder associated with an IL-10 deficiency and thus be within the scope of the claims. The disclosure also fails to set for the metes and bounds of what is encompassed within the definition of "activity" and "a disorder associated with an IL-10 deficiency". Thus the artisan would not know what responses Applicant intended to measure.

Claims 34 and 40 are indefinite because Applicant recites "modulating" in claim 34 and "alteration" in claim 40. However, Applicant fails to define how to evaluate the modulation or alteration. Although Applicant describes increasing the level of IL-10 by

IL-21 on p. 46, Applicant fails to define/specify what is/is not included within the limitations of the claims. The disclosure also fails to set for the metes and bounds of what is encompassed within the definition of "modulating" and "alteration". Thus the artisan would not know what responses Applicant intended to measure.

The rest of claims are dependent claims that depend from the claims discussed above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 9-12, 14, 29-34 are rejected under 35 U.S.C. 102 (e) as being anticipated by US Patent No. 6605272 (issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006).

US Patent No 6605272 teaches ZALPHA11 ligand, which is a novel cytokine having 100% identity to SEQ ID NO:2 (IL-21 of the instant application) as recited in the claims (see sequence search results as set forth below). '272 also teaches a potential therapeutic use of ZALPHA11 ligand, and agonist anti-ZALPHA11 receptor in several immunological disorders including multiple sclerosis as in claims 1-6, 9-12 and claims

29-33 (see col. 42, lines 9-31; col.192-198, claims 1-21.). '272 teaches administration of IL-21 to enhance an immune response (see col. 43, lines 19-43). '272 teaches that IL-21 enhances proliferation of $CD4^+$ T cells, $CD8^+$ cytotoxicity T cells and Natural killer cells and regulating production of cytokines such as increasing IL-10 decreasing IFN-γ to treat immunological disorders mediated by cellular immunity (see col.99-102, examples 41-42). The teachings of regulating immune responses of T cell proliferation and cytokines productions by administration of IL-21 meet the limitations of ameliorating a symptom of MS caused by inappropriate production of cytokines and cellular and humoral immune responses as recited in claims 1-4, 9-12, 29-31 and 34. The enhancing secretion of IL-10 and decreasing IFN-γ are evidenced by Wurster et al. (see p. 969, abstract; col. 2nd. Wurster et al. J. Exp. Med. 2002. 196:969-977 as in IDS). '272 also teaches an intravenous administration route as in claim 14 (see col.95, lines 40-55; table 6). '272 further teaches preparing a recombinant IL-21 polypeptide from mammalian cells and *E. coli* cells as in claims 32 and 33 (see col. 109, example 46; col.80-86, Examples 30-31).

The sequence search results disclose as follows:

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US-09-923-246-85
; Sequence 85, Application US/09923246
; Patent No. 6605272
; GENERAL INFORMATION:
;  APPLICANT: No. 6605272ak, Julia E.
;  APPLICANT:  Presnell, Scott R.
;  APPLICANT:  Sprecher, Cindy A.
;  APPLICANT:  Foster, Donald C.
;  APPLICANT:  Holly, Richard D.
;  APPLICANT:  Gross, Jane A.
;  APPLICANT:  Johnston, Janet V.
;  APPLICANT:  Nelson, Andrew J.
;  APPLICANT:  Dillon, Stacey R.
;  APPLICANT:  Hammond, Angela K.
;  TITLE OF INVENTION: NOVEL CYTOKINE ZALPHA11 LIGAND
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;  FILE REFERENCE: 99-16
;  CURRENT APPLICATION NUMBER: US/09/923,246
;  CURRENT FILING DATE:  2001-08-03
;  PRIOR APPLICATION NUMBER: EARLIER APPLICATION NUMBER: US/09/522,217
;  PRIOR FILING DATE: EARLIER FILING DATE: 2000-03-09
;  PRIOR APPLICATION NUMBER: EARLIER APPLICATION NUMBER: US 60/123,904
;  PRIOR FILING DATE: EARLIER FILING DATE: 1999-03-11
;  PRIOR APPLICATION NUMBER: EARLIER APPLICATION NUMBER: US 60/142,013
;  PRIOR FILING DATE: EARLIER FILING DATE: 1999-07-01
;  NUMBER OF SEQ ID NOS: 115
;  SOFTWARE: FastSEQ for Windows Version 3.0
; SEQ ID NO 85
;   LENGTH: 519
;   TYPE: PRT
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: MBP-human zalpha11 Ligand fusion polypeptide
US-09-923-246-85

  Query Match             100.0%;  Score 695;  DB 2;  Length 519;
  Best Local Similarity   100.0%;  Pred. No. 4.3e-71;
  Matches  131;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 QDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGN 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        389 QDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGN 448

Qy         61 NERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMIHQH 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        449 NERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMIHQH 508

Qy        121 LSSRTHGSEDS 131
              ||||||||||||
Db        509 LSSRTHGSEDS 519
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Therefore, Claims 1-4, 9-12, 14 and 29-34 are anticipated by US Patent No. 6605272.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6605272 (issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006) in view of US20030108549A (published Jun 12, 2003, priority date Oct 4, 2001) and Kawai et al. (Cell Immunol. 1996. 171:262-8).

US Patent No.6605272 teaches as set forth above but fails to teach an agonist anti-IL21R antibody as recited in claims 1, 5, 6, and an anti-inflammatory agent as in claims 7-8 and also fails to teach the administration routes including intrathecal injection and administration to CSF in claims 13-15.

US20030108549 ('549) teaches IL21/IL21R agonists including an IL21 polypeptide and an agonist anti-IL21R antibody (see p. 3 [0023], p.5 [0041]). '549 teaches using a combination of anti-inflammatory agent and an IL-21/IL21R agonist to treat T cell-mediated diseases such as tumor (see p.3 [0024], p.5 [0039], [0040], [0208]). '549 also teach using an IL-21/IL21R agonist in enhancing T cell proliferation and cytokine regulation ([0327], Examples 9-11). The teachings of US20030108549 provide a motivation of using a composition comprising an anti-inflammatory agent and

IL-21 to enhance and regulate immune responses in treating different immunological diseases including multiple sclerosis since the composition comprising anti-inflammation agent and IL-21 can effectively regulate immune responses including T cell proliferation and cytokine regulation.

Kawai et al. teach a method of administering monoclonal antibodies that are against LFA-1 and ICAM-1 in EAE rat model by intracerebroventricular and intrathecal administration routes as in claims 13-15 (see p. 262, abstract and p. 263 materials and methods). Administration of agents (IL21 agonists) to the cerebrospinal fluid (CSF) as in claim 15 is a result of intrathecal administration because of the nature of neuroanatomy. Drugs administered by intrathecal injection would eventually diffuse to CSF. The teaching of Kawai et al. provides a motivation and expectation of success in delivering agents to the EAE rat model by intrathecal administration.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to be motivated and have expected success in ameliorating the symptom of multiple sclerosis caused by inappropriate production of IL-10 and IFN-γ by using a composition comprising an anti-inflammatory agent and an agonist of IL-21/IL21 including the IL-21 polypeptide of SEQ ID NO:2 and an agonist anti-IL21R antibody because a composition of an anti-inflammatory agent and IL-21 has been successfully used to regulate immune responses of T cell proliferation and cytokine regulation. The person of skill in the art would have been motivated to do so because IL-21 inhibits production of IFN-γ from developing Th1 cells leading to reducing the inflammation of MS. In addition, it would also have been obvious to one of ordinary skill

in the art at the time the instant invention was made to be motivated and have expected success in administering a composition comprising an anti-inflammatory agent and an agonist of IL-21/IL21R including the IL-21 polypeptide of SEQ ID NO:2 and an agonist anti-IL21R antibody to the central nervous system by intrathecal injection or administering the agonist of IL-21/IL21R into CSF because administration of monoclonal antibodies to an EAE animal model by intrathecal injection.

Claims 1-19, 29-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. Patent No.6605272, US20030108549 (published Jun 12, 2003, priority date) Kawai et al. (Cell Immunol. 1996. 171:262-8) as applied in claims 1-15, 29-34 above and further in view of Beebe et al. (Cytokine & Growth Factor Rev. 2002. 13: 403-12 as in IDS submitted on 05/23/06).

US Patent No.6605272, US20030108549 and Kawai et al. teach as set forth above but fail to teach evaluating the level of IL-10 in patients with multiple sclerosis as in claims 16-19 and 34-40.

Beebe et al. teach that IL-10 has an anti-inflammatory and immunosuppressive effect on pro-inflammatory function of T helper cells and natural killer cells. Beebe et al teach that a low level of IL-10 was found prior to disease relapse in autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS) (see p. 407, sections 8-9). Beebe et al. further teach that the elevated levels of IL-10 found in MS patients who are successfully treated with IFN-β (see p.407, 1st col, 2nd paragraphs). The teachings of Beebe et al. provide a motivation to evaluate the level of IL-10 and to evaluate the effect

of administration of an agonist of IL-21/IL-21R to MS patients because low production of IL-10 is found in MS and EAE, and successful treatment of MS patients of MS would induce the production of IL-10 in patients as in claims 16-19 and 34-40. Thus, it would have been obvious for one of ordinary skill in the art to be motivated and have expected success in ameliorating a symptom of MS regulated by inappropriate production of IL-10 and IFN-γ by incorporating the teachings of Beebe et al. to measure/monitor the levels of IL-10 in MS patients while treating patients with IL-21 agonist/ agonist anti-IL-21R antibodies since low production of IL-10 is found in MS and EAE, and successful treatment of MS patients would induce the production of IL-10 in patients . It would also have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated and would have expected success in modulating a disorder associated with an IL-10 deficiency or immunological disorder such as MS because MS has been shown to be associated with lower level of IL-10 and successful treatment of MS would induce the production of IL-10.

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

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AAE14934
ID   AAE14934 standard; protein; 162 AA.
AC   AAE14934;
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DT 27-AUG-2003 (first entry)
DE Human interleukin-21 (IL-21) antagonist #2.
KW Interleukin-21; IL-21; antagonist; cancer; inflammatory; autoimmune disorder; rheumatoid arthritis; multiple sclerosis; systemic lupus erythematosus; myasthenia gravis; diabetes; human; zalpha11 ligand; mutant; mutein.
OS Homo sapiens.
Synthetic.
FH Key Location/Qualifiers
FT Misc-difference 145
/note= "Wild-type Gln substituted with Asp"
Misc-difference 148
/note= "Wild-type Ile substituted with Asp"
PN WO2003040313-A2.
PD 15-MAY-2003.
PF 28-OCT-2002; 2002WO-US034502.
PR 05-NOV-2001; 2001US-0337586P.
PA (ZYMO) ZYMOGENETICS INC.
PI Presnell SR, West JW, Novak JE;
DR WPI; 2003-441547/41.
N-PSDB; AAD47854.
PT New IL-21 polypeptide and encoding polynucleotide, useful for diagnosing and treating disorders with aberrant expression or activity of the IL-21 polypeptide, such as cancer, rheumatoid arthritis, multiple sclerosis and diabetes.
PS Claim 3; Page 58; 71pp; English.
CC The invention relates to polynucleotides and polypeptides of interleukin-21 (IL-21) antagonists, that bind with specificity and exhibit an EC50 that is not detectable in receptor binding studies. The antagonists of the invention have mutations in the D helix of the IL-21 molecule, and can be used to inhibit the activity of IL-21 with its cognate receptor. The IL-21 antagonists are useful for diagnosing and treating disorders involving the aberrant expression or activity of the IL-21 polypeptide, such as cancer, inflammatory and autoimmune disorders, including rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis and diabetes. The polypeptides can also be used to prepare antibodies that bind IL-21 epitopes, peptides or polypeptides, and for enhancing in vivo killing of target tissues. The present sequence is human IL-21 antagonist. The antagonist molecule is a mutant of IL-21 polypeptide, with Gln145Asp and Ile148Asp substitutions. The resulting mutant was designated zalpha11 ligand Q153D/I156D
SQ Sequence 162 AA;

Query Match 98.3%; Score 683; DB 7; Length 162;
Best Local Similarity 98.5%; Pred. No. 1.6e-70;
Matches 129; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

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Qy          1 QDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGN 60
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Db         32 QDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGN 91

Qy         61 NERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMIHQH 120
              |||||||||||||||||||||||||||||||||||||||||||||||||||| || |||
Db         92 NERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLDKMDHQH 151
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Qy        121 LSSRTHGSEDS 131
              ||||||||||||
Db        152 LSSRTHGSEDS 162


US-10-282-622-6
; Sequence 6, Application US/10282622
; Patent No. 6929932
; GENERAL INFORMATION:
;  APPLICANT: Presnell, Scott R.
;  APPLICANT:  West, James W.
;  APPLICANT:  No. 6929932ak, Julia E.
;  TITLE OF INVENTION: ZALPHA11 LIGAND ANTAGONISTS
;  FILE REFERENCE: 01-37
;  CURRENT APPLICATION NUMBER: US/10/282,622
;  CURRENT FILING DATE:  2002-10-28
;  PRIOR APPLICATION NUMBER: 60/337,586
;  PRIOR FILING DATE: 2001-11-05
;  NUMBER OF SEQ ID NOS: 30
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 6
;   LENGTH: 162
;   TYPE: PRT
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: zalpha11 ligand Q153D/I156D
US-10-282-622-6

  Query Match             98.3%;  Score 683;  DB 2;  Length 162;
  Best Local Similarity   98.5%;  Pred. No. 2.3e-70;
  Matches  129;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps
0;

Qy          1 QDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGN 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         32 QDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGN 91

Qy         61 NERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMIHQH 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||| || |||
Db         92 NERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLDKMDHQH 151

Qy        121 LSSRTHGSEDS 131
              ||||||||||||
Db        152 LSSRTHGSEDS 162
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Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
November 30, 2006

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